Remarks

With entry of the amendment, claims 22-25 are pending in the application. In the Office Action mailed July 3, 2002, independent claims 21, 40, and 51, and claims 22-33, 41-50, and 52-54, which depend directly or indirectly from claims 21, 40, or 51, respectively, are drawn to methods of simultaneously determining alleles. Independent claims 34 and 55, and claims 35-39, which depend from claim 34, are drawn to kits for simultaneously analyzing short tandem repeat (STR) sequences. Claims 21-55 are objected to as containing more than one period; claim 28 is rejected under 35 U.S.C. 112, second paragraph; claims 21, 26-34, 39, 48-51, and 53-55 are rejected under 35 U.S.C. 102(e); claims 21, 23, 26, 29-31, and 48 are rejected under 35 U.S.C. 102(a); claims 21-55 are rejected under 35 U.S.C. 103(a); claims 21, 22, 26-34, 39, and 48-55 are rejected under the judicially created doctrine of obviousness-type double patenting; and claims 1-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting.

In view of the amendments above and arguments below, Applicants request reconsideration and allowance of the claims. All amendments are fully supported by the specification and introduce no new matter.

Objection to claims

Claims 21-55 were objected to as containing more than one period. Applicants have cancelled claims 21 and 26-55 and have rewritten claims 22-25, which formerly depended from claim 21, as independent claims. The amendment overcomes the rejection.

Rejection under 35 U.S.C. 112, second paragraph

Claim 28, which depends from claim 21, is rejected as being indefinite for the recitation of step (e), which lacks an antecedent basis in claim 21. Applicants have cancelled claim 28 without prejudice to filing a continuation application thereon, rendering moot the rejection.

Rejection under 35 U.S.C. 102(e)

Claims 21, 26-34, 39, 48-51, and 53-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Schumm *et al.* (US Patent No. 5,783,406) and Schumm *et al.* (US Patent No. 5,674,686). Applicants have cancelled these claims without prejudice, thereby rendering moot the rejection.

Rejections under 35 U.S.C. 102(a)

Claims 21, 23, 26, 29-31, and 48 are rejected as being anticipated by Schumm *et al.* (Fourth International Symposium on Human Identification, 1993). Schumm *et al.* is said to teach a method for rapid and easy interpretation of DNA STR markers. Schumm *et al.* shows fluorescein-labeled loci CSF1PO, TPOX, TH01, and vWF amplified by multiplexing and separated by electrophoresis. The Schumm *et al.* publication has different authors (James W. Schumm, Ann Lins, Christoph

Puers, and Cindy Sprecher) than the inventive entity of the instant application (James W. Schumm, Cynthia (Cindy) J. Sprecher, and Ann M. Lins). Applicants have cancelled claims 21, 26, 29-31, and 48 without prejudice. Pursuant to C.F.R. 1.132, Applicants submit herewith the declaration of Cynthia J. Sprecher, in which she attests to the fact that she, Schumm, and Lins were co-authors on the Schumm *et al.* publication. As stated in the Sprecher declaration, the publication describes the work of Schumm, Lins, and Sprecher. Mr. Puers, the only co-author on the Schumm *et al.* publication who is not an inventor on the instant application, contributed technical support, but did not make an inventive contribution to the claimed invention. Applicants respectfully request that the rejection under 35 U.S.C. 102(a) be withdrawn.

Rejections under 35 U.S.C. 103(a)

Freugeau *et al.*

Claims 21, 26, 27, 29-31, 33, and 48-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fregeau *et al.* (BioTechniques, 1993). The Examiner characterizes Fregeau as teaching DNA typing with fluorescently tagged STRs in a multiplex system containing HUMCD4, HUMFABP, and HUMCATBP2. Fregeau was said to demonstrate that primers for HUMHPRT, HUMTH01, HUMARA, HUMCD4, HUMFABP, HUMPLA2A1, and HUMRENA4 were used to amplify DNA, as well as primers identical to SEQ ID NO:1, 2, 9, 15, 16, 19, 20, 27, 28, and 30. Fregeau was also characterized as teaching multiplexing HUMvWF, HUMFABP, HUMACTBP2, and D21211. Fregeau was said to teach that: loci HUMCD4, HUMARA, and HUMTH01 have the same optimal annealing temperature; a four STR system using HUMCD4, HUMHPRT, HUMTH01, HUMARA was explored; HUMHPRTB, HUMTH01, HUMCD4, HUFABP, and HUMPLA2 were co-amplified in a multiplex.

The Examiner acknowledges that Fregeau does not teach multiplex reactions including the specifically recited combinations of STR loci. However, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to perform the experiment taught by Fregeau to obtain the claimed invention. The Examiner reasons that the skilled artisan would have been motivated to combine the loci taught by Fregeau to make additional combinations of loci suitable for identifying alleles simultaneously because Fregeau teaches all of the conditions necessary for multiplex coamplification and provides a reasonable expectation of success by showing multiplex amplification of a number of different STRs.

Applicants have cancelled claims 21, 26, 27, 29-31, 33, and 48-55 without prejudice, rendering moot this rejection.

Caskey and Kimpton (Int. J. Leg. Med.) in view of Kimpton or Fregeau or Urquhart

Claims 21-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caskey (U.S. Patent No. 5,364,759) and Kimpton (Int. J. Leg. Med. 106:302-311, 1994) in view of Kimpton (PCR Methods and Applications) or Fregeau or Urquhart (Int. J. Leg. Med. 107:13-20, 1994).

The Examiner characterized Caskey as disclosing amplifying STR sequences and evaluating the amplification products for identification, identifying STR loci by searching GenBank, strategies for determining sequences flanking STRs, using different labels to overcome the problem of identifying overlapping alleles, and primers for amplifying HUMFABP, HUMPRTB, and HUMTH01. The Examiner acknowledged that Caskey fails to teach the specific combinations of loci recited in the claims.

The Examiner characterized Kimpton (Int. J. Leg. Med.) as disclosing a multiplex amplification of four tetrameric STR loci and adjusting most of the conditions of the multiplex system to optimize results. The Examiner acknowledged that Kimpton fails to teach the specific combinations of loci recited in the claims.

Fregeau is cited as teaching a multiplex system containing HUMCD4, HUMFABP, and HUMCATBP2, as well as demonstrating that primers for STR systems HUMHPRT, HUMTH01, HUURA, HUMCD4, HUMFABP, HUMPLA2A1, and HUMRENA4 were used to amplify genomic DNA. Fregeau was also characterized as teaching that HUMvWF, HUMFABP, HUMACTBP2, and D21S11 have the same annealing temperature and to permit multiplex amplification. Fregeau was further characterized as teaching that HUMCD4, HUMARA, and HUMTH01 have the same optimal annealing temperature, Fregeau was said to teach a four STR system consisting of HUMD4, HUMHPRT, HUMTH01, and HUMARA, and multiplex amplification of polymorphic STR loci including HUMHPRTB, HUMTH01, HUMCD4, FUMFABP, and HUMPLA2A. Fregeau was also characterized as teaching a specific annealing temperature for each STR system, and as discussing the advantages of STR analysis.

Kimpton (PCR Methods and Applications) was characterized as teaching multiplex amplification of STR loci including HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYAR03, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2, and D21S11, as well as primers for amplifying HUMACTBP2, HUMAPOAII, HUMFABP, HUMTH01, and HUMvWA31/A identical to DEQ ID NO: 1, 4, 15, 27, and 32. Kimpton is also cited as teaching optimization of multiplexing parameters.

The Examiner characterized Urquhart as teaching a method of simultaneously determining the alleles present in at least two STR loci and amplification of HUMVWFA31, HUMTH01, HUMF13A01, HUMFES/FPS, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04,

HUMTFIIDA, HUMFABP, HUMGABRB15, and HUMD21S11.

The Examiner concluded that, although the art does not combine to teach the particular combinations of loci recited in the claims, it would have been prima facie obvious to modify the teachings of Caskey and Kimpton with the loci of Fregeau, Kimpton, or Urquhart to obtain the claimed invention based on the teachings of Caskey and Kimpton, because Fregeau, Kimpton, or Urquhart provide motivation to choose any reasonable number of loci in desired combinations, and implement multiplex amplification thereof by routine optimization of PCR methodology.

Applicants respectfully submit the combination of references does not teach or suggest the method of any of claims 22-25. As the Examiner acknowledged, the references do not combine to teach the specific combination of loci recited in the claimed invention. In fact, the references indicate that the selection of STR loci that can be co-amplified is not a trivial matter, but rather, one that would require a considerable amount of experimentation.

Caskey identified only two sets of STR loci used in multiplex analysis, one of which was reported by Caskey *et al.* as producing problematic overlapping doublet bands on gel electrophoresis.

Kimpton teaches that STR loci must be selected carefully to avoid anomalous banding caused by 'slippage' or other amplification artifacts.

Fregeau identifies loci having optimal annealing temperatures, and teaches that optimal annealing temperatures to identify STR monoplex systems that <u>may</u> be useful in multiplex amplification. However, the empirical annealing temperature teaching of Fregeau *et al.* does not teach or suggest the method of multiplex amplification of any of claims 22-25. In fact, the teachings of Fregeau do not provide a reasonable expectation that the particular claimed loci would be useful in multiplexing, because Fregeau teaches that STR loci selected for multiplexing based on empirical annealing temperatures may have allele size ranges that are not mutually resolvable, and consequently, the results are unpredictable. Applicants respectful submit that the mere knowledge that multiplex amplification and analysis of STR loci offers advantages over monoplex amplification and analysis does not suggest which STR loci could be co-amplified.

Applicants respectfully submit that Kimpton (PCR Methods) does not provide guidance as to selection of STR loci, let along the particular combinations of loci recited in any of claims 22-25, other than to note that "tri-, tetra, and pentanucleotide STR loci appear to be well suited for routine identification of individuals." In view of the number of possible combinations of tri-, tetra, and pentanucleotide STR loci in the human genome, Kimpton does not combine with Caskey and Kimpton *et al.* (Int. J. Leg. Med.) to teach the present claimed invention.

Applicants disagree with the Examiner's characterization of Urquhart. Urquhart *et al.*

reported the results of a survey of twelve STR loci (HUMVWFA31, HUMTH01, HUMF13A01, HUMFES/FPS, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFABP, HUMGABRB15, and HUMD21S11) in which the loci were tested individually to determine their suitability for use in forensic identification. Of the twelve loci, only four (HUMFEX/FPS, HUMTH01, HUMF13A01, and HUMMVWFA31 were suitable candidates for multiplex amplification and analysis. Urquhart does not cure the deficiencies of the primary references.

Caskey in view of GenBank STR loci

Claims 21-55 were rejected under 35 U.S.C. 103(a) as being unpatentable over Caskey in view of GenBank STR loci HUMTH01, HUMTPOX, HUMF13A01, HUMFABP, HUMMYPOK, HUMBFXIII, HUMHPRTB, HSAC04, HUMCYP19, and HUMPLA2A1. Caskey is cited for the reasons summarized above. Caskey is quoted asserting knowledge of the sequence of an STR and its flanking sequences permit primer design and synthesis. Caskey is further said to describe the empirical nature of multiplex amplification reactions and optimization. STR loci HUMTH01, HUMTPOX, HUMF13A01, HUMFABP, HUMMYPOK, HUMBFXIII, HUMHPRTB, HSAC04, HUMCYP19, and HUMPLA2A1 are disclosed in GenBank.

As discussed above, Caskey disclosed only two multiplexes (duplexes), one of which produced overlapping alleles. Caskey provides no teaching as to which loci could be amplified to produce results that could be evaluated in any meaningful way. Clearly, the GenBank sequences do not cure the deficiencies of Caskey.

In view of the foregoing, Applicants respectfully request that the rejection of claims 22-25 under 35 U.S.C. 103(a) be withdrawn.

Rejections under the judicially-created doctrine of obviousness-type double patenting

Claims 21, 26-31, 33, 34, 39, 48-51, and 53-55 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,783,406, which require co-amplifying HUMCSF1PO, HUMFESFPS, and HUMTH01. Claims 21, 26-31, 50, 51, 53, and 55 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,674,686, which requires co-amplifying HUMCSF1PO, HUMFESFPS, and HUMTH01. Claims 21, 26-31, 33, 34, 39, 48-51, and 53-55 have been cancelled without prejudice, rendering moot this rejection.

Claims 21, 22, 26-34, 39, and 48-55 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 6,221,598. Claims 21, 26-34, 39, and 48-55 have been cancelled without prejudice, rendering moot this rejection as it applies to those claims. Applicants respectfully traverse the rejection of claim 22

as being obvious over claims 1-43 of U.S. Patent No. 6,221,598. However, in the interest of advancing prosecution on the merits, Applicants submit herewith a terminal disclaimer for U.S. Patent No. 6,221,598, accompanied by the appropriate fee required under 37 C.F.R. 1.321

This amendment is accompanied by a Request for a Three-Month Extension of Time, a Terminal Disclaimer, and check number _____ in the amount of $1,040.00 to cover the fees required under 37 C.F.R. 1.321 and 37 CFR 1.17(a)(3). No other fee is believed due in connection with this submission. Please charge any additional fee due or credit any overpayment of fees to Deposit Account No. 50-0842.

As the application is now in condition for allowance, Applicants respectfully request withdrawal of the rejections and allowance on the claims.

Respectfully submitted,

Date: January 3, 2002

Jill A. Fahrlander
Reg. No. 42,518

Docket No.: 016026-9238
Michael Best & Friedrich LLP
One South Pinckney Street
P. O. Box 1806
Madison, WI 53701-1806
(608) 257-3501

MARKED UP VERSION SHOWING THE CHANGES

22. A [The] method of simultaneously determining the alleles present in [claim 21 wherein the set of] at least [two] three short tandem repeat loci [co-amplified therein is a set of at least three loci selected] from one or more DNA samples, [the group consisting of] comprising:

(a) obtaining at least one DNA sample to be analyzed;

(b) selecting a set of at least two three tandem repeat loci of the DNA sample to be analyzed which can be amplified together, wherein the at least three short tandem repeat loci in the set comprises at least three loci selected from the group consisting of:

HUMTPOX, HUMVWFA31 and HUMCSF1PO;
HUMHPRTB, HUMFESFPS and HUMVWFA31;
HSAC04 (ACTBP2), HUMCYP19 and HUMPLA2Al;
HUMAPOA2, HUMCYP19 and HUMPLA2Al;
HUMCD4, HUMCSF1PO and HUMTH01;
HUMCYP19, HUMFABP and HUMPLA2Al;
HUMCYP19, HUMHPRTB and HUMPLA2Al;
HUMHPRTB, HUMFESFPS and HUMLIPOL;
HLTMF13A01, HUMFABP and HUMCD4;
HUMHPRTB, HUMBFXIII (Fl3B) and HUMPLA2A1;
HUMHPRTB, HUMBFXIII (F13B) and HUMTPOX;
HUMHPRTB, HUMBFXIII (F13B) and HUMFESFPS;
HUMBFXIII (F13B), HUMFESFPS and HUMLIPOL;
HUMCSF1PO, HUMTPOX and HUMCD4;
HUMHPRTB, HUMFESFPS and HUMMYOPK (Myotonic);
HUMCSF1PO, HUMTH01 and HUMCD4;
HUMCSF1PO, HUMTH01 and HUMVWFA31; and
HUMHPRTB, HUMBFXIII (Fl3B) and HUMLIPOL;

(c) co-amplifying the set of at least three short tandem repeat loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set; and

(d) evaluating the amplified alleles in the mixture to determine the alleles present at each of the co-amplified loci in the set.

23. A [The] method of [claim 21 wherein] simultaneously determining the alleles present in [co-amplified therein is the set of] at least [two] three short tandem repeat loci from one or more DNA samples, [is a set of at least three loci] comprising:

(a) obtaining at least one DNA sample to be analyzed;

(b) selecting a set of at least three short tandem repeat loci of the DNA sample to be analyzed which can be amplified together, wherein the at least three short tandem repeat loci in the set comprises HUMTPOX, HUMTH01 and HUMCSF1PO;

(c) co-amplifying the set of at least three short tandem repeat loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set; and

(d) evaluating the amplified alleles in the mixture to determine the alleles present at each of the co-amplified loci in the set.

24. A [The] method of [claim 21 wherein] simultaneously determining the alleles present in the [set of] at least four [two] short tandem repeat loci [co-amplified therein is a set of at least four loci selected] from one or more DNA samples, comprising [the group consisting of]:

(a) obtaining at least one DNA sample to be analyzed;

(b) selecting a set of at least four short tandem repeat loci of the DNA sample to be analyzed which can be amplified together, wherein the at least four short tandem repeat loci in the set comprises at least four loci selected from the group consisting of: HUMHPRTB, HUMFESFPS, HUMBFXIII (FI3B) and HUMLIPOL; and HUMCSF1PO, HUMTPOX, HUMTH01, and HUMCD4;

(c) co-amplifying the set of at least four short tandem repeat loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set; and

(d) evaluating the amplified alleles in the mixture to determine the alleles present at each of the co-amplified loci in the set.

25. A [The] method of [claim 21 wherein] simultaneously determining the alleles present in [the set of] at least [two] four short tandem repeat loci from one or more DNA samples, [co-amplified therein is a is a set of at least four loci] comprising:

(a) obtaining at least one DNA sample to be analyzed;

(b) selecting a set of at least four short tandem repeat loci of the DNA sample to be analyzed which can be amplified together, wherein the at least four short tandem repeat loci in the set comprises HUMCSF1PO, HUMTPOX, HUMTH01 and HUMVWFA31;

(c) co-amplifying the set of at least four short tandem repeat loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set; and

(d) evaluating the amplified alleles in the mixture to determine the alleles present at each of the co-amplified loci in the set.